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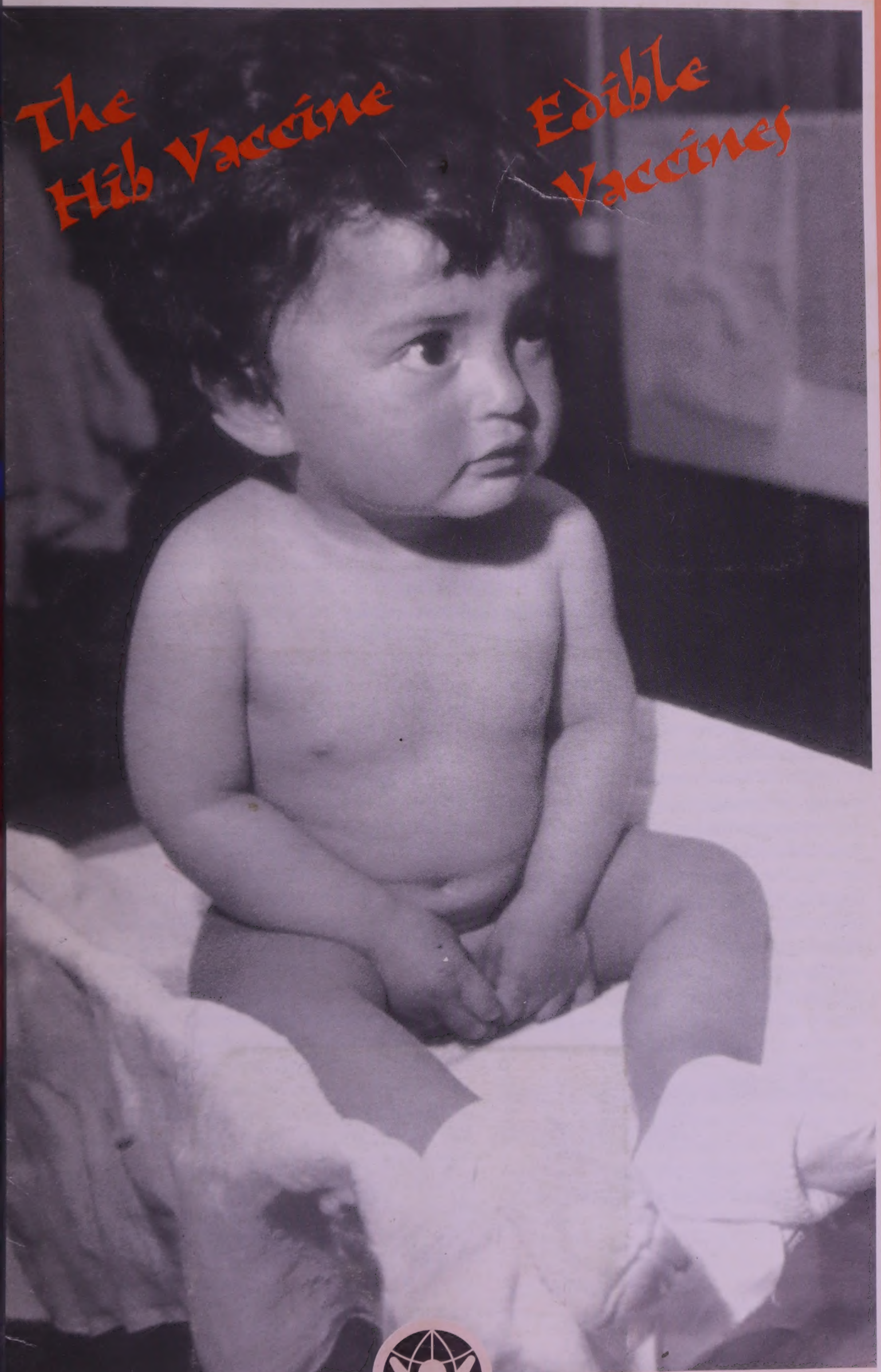

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In this issue

The CVI seeks speedy Third World adoption of Hib vaccine

A vaccine that has almost wiped out one important cause of two life-threatening diseases in the industrialized world is now ready to be launched massively in the developing world, where it could prevent at least a quarter of a million deaths – and perhaps even twice that number – in children every year.

The vaccine is one of a new breed of so-called conjugate vaccines that protect against the bacterium *Hæmophilus influenzæ* type b (Hib), which is responsible for many cases and deaths from pneumonia and meningitis. The Hib conjugate vaccine has almost cleared western Europe, North America, and Oceania of severe Hib disease, according to a CVI report.[1]

The CVI has enlisted the help of experts from around the world to put together an agenda that draws on the work carried out by many groups over the past decade on Hib disease and that spells out the steps needed to hasten the wider launch of the vaccine.

In the U.S., where the first Hib conjugate vaccine was licensed in 1987, routine vaccination has slashed annual case numbers by over 99% – from around 20,000 in the mid-1980s to less than 82 laboratory-confirmed cases in 1994[2,3] – at an estimated annual savings of nearly $400 million a year.

"There is no question in my mind that this vaccine is ready for wider use," says CVI Executive Secretary Dr Jong-Wook Lee. "The question now is: are the developing countries ready?"

The first Hib vaccine to appear – in the U.S. again, in the mid-1980s – had a major drawback: it was ineffective in children under 2 years of age – the age-group, at least in developing countries, most affected by invasive Hib disease (83% of Hib meningitis, for example, occurs before one year of age in the Gambia). But not an unexpected drawback, since this vaccine relied for its immunostimulant (immunogenic) action solely on the outer capsule of the bacterium, consisting of a sugar molecule (polysaccharide) called polyribosyl phosphate (PRP), which is a notoriously ineffective vaccinating antigen in young infants.

The Hib conjugate vaccines, so-called because they link (conjugate) PRP to a powerfully immunogenic "carrier" protein, such as the chemically inactivated toxins (toxoids) of the diphtheria or tetanus bacteria, provoke a stronger, more complete immune response.

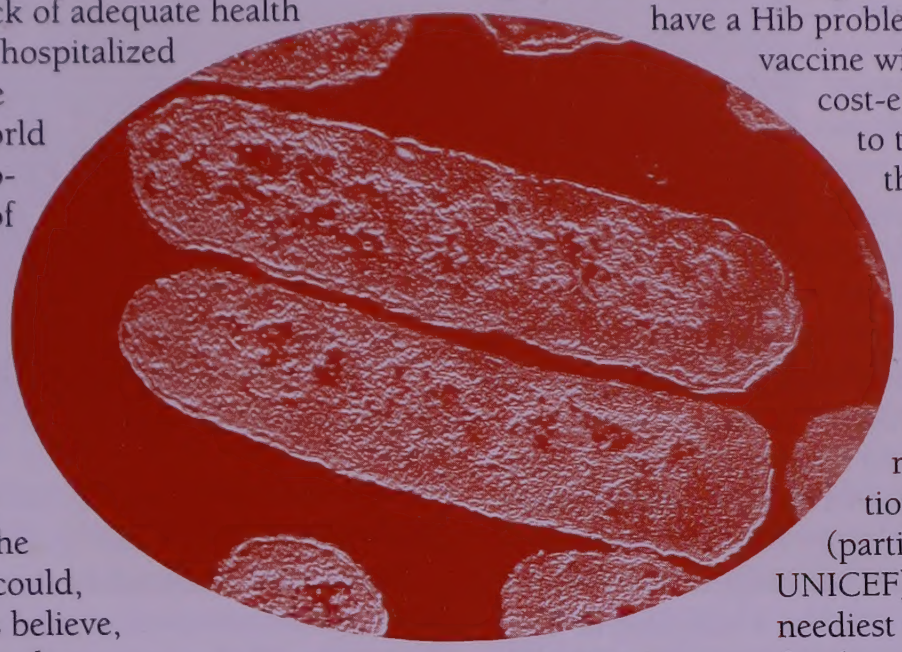
One of the main public health assets of the conjugate vaccine is its ability to prevent the bacterium from setting up home in the nose and throat (nasopharynx) of its host, and staying there quite happily for months without causing disease. About 1-4% of children in industrialized countries and up to 33% in developing countries are unwitting Hib carriers – and, more importantly for the community at large, potential Hib spreaders. (Only a fraction of people carrying the organism actually come down with invasive disease.) By reducing – or possibly even clearing – nasopharyngeal carriage, the vaccine seems to create a state of herd immunity in a community that hampers transmission of the bug. In the U.S., for example, herd immunity reduced the incidence of meningitis in unimmunized infants by 40%. The original unconjugated PRP vaccine did not induce herd immunity.

Before the advent of Hib vaccines, treatment with antibiotics was the only way to alleviate the burden of Hib disease. Treatment reduced Hib deaths by up to 40% in industrialized countries. In developing countries, treatment has been the mainstay

The Children's Vaccine Initiative (CVI) is a coalition of international and national agencies, national governments, non-governmental organizations, and public- and private-sector vaccine companies. It was established in 1991 to promote, coordinate and accelerate the development and introduction of improved and new vaccines and thereby enhance the protection of the world's children against infectious diseases.

Cover photo: UNICEF/P. McCloskey

of attempts to control acute respiratory infections and in some places was able to reduce mortality from these infections by up to 60%. One problem with treatment is the growing resistance of Hib to antibiotics in many parts of the developing world. Another is the lack of adequate health care – 20% of hospitalized children in the developing world die of pneumonia and 40% of meningitis. And setting up or maintaining the infrastructure needed to provide good treatment in the Third World could, many analysts believe, cost more than the logistics and resources needed for vaccination. But for most public health policy makers, the overriding argument in favour of vaccination is its proven ability in industrialized countries to bring the incidence of Hib disease down to near-zero within three or four years of its introduction.



***Hæmophilus influenzæ* type b (Hib).** Photo: CNRI

Indeed, in those countries the Hib conjugate vaccines have demonstrated their efficacy (over 90% of vaccinated people protected against disease under well-controlled study conditions), effectiveness (over 95% of children protected in a real-life or "field" setting) and impact (over 99% reduction in incidence of disease).

As CVI Coordinator Dr Roy Widdus puts it: "The Hib conjugate vaccine has clearly shown itself to be an extremely safe and powerful public health tool against a microbe that used to threaten millions of children in the industrialized world. It's time now to get it as quickly as possible into the developing world, where hundreds of thousands of young children and infants are still dying of disease caused by the microbe."

The Third World's turn

So, what, you might ask, are we waiting for?

Getting the Hib vaccine into the Third World means convincing countries that they have a Hib problem, that the vaccine will provide a cost-effective solution to the problem and that they should give the problem priority status. It means convincing the donor community and international agencies (particularly UNICEF) to help the neediest countries to pay for the vaccine. It means convincing the WHO's Global Programme for Vaccines and Immunization (GPV) and more especially, the GPV's Expanded Programme on Immunization (EPI) – to help countries with the logistics and management of getting the vaccine to the children who need it.

"We're talking about information – getting it, communicating it and turning it into action," says Dr Widdus. "That's what the Hib agenda is all about."

The agenda calls for answers to four major questions: How big a problem is Hib disease in the Third World? How effectively would the Hib vaccines combat the problem? How cost-effectively would they do so? How can countries that could benefit from the vaccine be helped to get it and use it?

How big a problem is Hib in the developing world?

In the industrialized world, a large number of epidemiological studies have provided information on the annual incidence of invasive Hib disease (34-130 cases per 100,000 children under five years of age) and this information spurred public health authorities to adopt Hib vaccination.

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By contrast, in developing countries, outside a few initiate circles, Hib is often unheard of, unthought of, undiagnosed and, generally, submerged under the surrounding deluge of childhood disease and death. Undiagnosed, too, because diagnosis of Hib disease – particularly Hib pneumonia – requires relatively sophisticated bacteriological laboratory and hospital resources that are lacking in most parts of the developing world.

Whatever the cause, though, lack of awareness of Hib disease is one reason why developing countries have not been clamouring for a vaccine. What very limited data there are, from nine developing countries, shows the incidence of invasive Hib disease in the Third World ranging so widely – from 20 per 100,000 under five-year-old children in Argentina to 104 per 100,000 among South African blacks (a range not so different from that revealed by a sampling of 15 studies in 13 industrialized countries) – as to be of little help to any of the remaining 130 developing countries debating the wisdom of introducing Hib vaccination. There is, however, some evidence that mortality from Hib meningitis is greater – and occurs in younger age-groups – in developing than in industrial countries.

In the early years of this decade, before work on the Hib agenda had begun, the GPV's vaccine research and development unit (VRD) recognized the need to do something about the paucity of epidemiological data on Hib disease in the developing world. VRD researchers, together with scientists from the U.S. Centers for Disease Control and Prevention (CDC), began work on designing a so-called generic protocol, that developing countries could use to define their burden of Hib disease. One such protocol, concerning the burden of Hib meningitis, is now available[4].

Concern over lack of reliable data on Hib disease is reflected in the agenda, which calls for surveillance for invasive Hib infections, including the necessary laboratory and other logistical backup. Studies, using for example the VRD protocol, are needed most urgently in areas of the world where no information is available or where health authorities are sceptical about the need for a Hib vaccine. Priority areas include Asia, the ex-Soviet Union countries, North Africa and Eastern Europe.

Will a Hib vaccine be safe and effective in the Third World?

There are two indications that the answer could well be a double "yes."

One comes from Santiago, Chile, where a Hib conjugate vaccine administered to 38,741 infants at two, four and six months of age protected 90% of them against all invasive Hib disease, 91% against Hib meningitis and 80% against Hib pneumonia.

The vaccine, licensed by the Chilean health authorities, was administered through the regular Chilean primary health care system. It was given in the same syringe with the diphtheria-tetanus-pertussis (DTP) combination, with no adverse effects on the safety or potency of the vaccine "cocktail" or any of its components. Following this pilot application and its analysis[5] by Chilean health officials and scientists from the University of Maryland's Center for Vaccine Development in the U.S., on July 1 this year the Chilean health authorities gave the go-ahead for a nationwide launch of the vaccine. Two other Latin American countries, Costa Rica and Uruguay, have already incorporated the vaccine into their routine immunization programmes.

The second indication that the Hib conjugate vaccine can be effective under Third World conditions comes from a study (in press) conducted in the Gambia between 1993 and 1995 by the United Kingdom's Medical Research Council. Given to over 20,000 children at 11, 18 and 24 weeks of age, the vaccine protected almost all of them against invasive Hib disease and greatly reduced the proportion carrying Hib without symptoms of disease. A six-month extension of the study, made possible through a grant from the CVI and other sources, showed that vaccination had also greatly lowered the incidence of X-ray

M. Weber

Baby receiving the Hib conjugate vaccine in the Gambia trial

confirmed cases of pneumonia, of whatever cause. This finding, says Dr Kim Mulholland, a leading member of the study team and now with the WHO's Division of Child Health and Development, is "very exciting: it tells us not only that the vaccine works but for the first time gives us an indication that in a Third World setting a significant proportion of all pneumonia could be due to Hib." Applying that proportion to the widely accepted estimate of 3-3.5 million bacterial pneumonia deaths annually suggests, says Dr Mulholland, that Hib may be causing more than 600,000 pneumonia deaths a year – just about double the "working estimate" that health statisticians have been using so far.

Dr Mulholland also believes the 40,000 or so meningitis deaths generally blamed on Hib could also be doubled. This figure, he says, is based on an average case fatality rate – the risk of an afflicted person dying – of 18%. "In the Gambia, about 30% of children with Hib meningitis die even with reasonable treatment and just about 100% without treatment. Add 80,000 Hib meningitis deaths to at least 600,000 Hib pneumonia deaths and we're talking about somewhere in the order of 700,000 Hib deaths a year."

Clearly, though, information is needed about how the vaccine would fare in a wider variety of Third World settings. To help countries to make their own assessments, the Hib agenda cites the need for a generic protocol – plus the necessary lab infrastructure – for testing the safety and immunogenicity of a Hib vaccine. It also advocates a close look at the comparative usefulness of the different formulations of the Hib vaccine (liquid, freeze-dried, conjugated with this or that carrier), in different combinations (with DTP or the hepatitis B vaccine), in different dosage regimens (two instead of the current three doses) and delivered through different systems (as part of an EPI national immunization programme, with its cold chain and other logistical trappings, or not).

How cost-effective would a Hib vaccine be in the Third World?

A Hib conjugate vaccine used in developing countries, costing $1 a dose for the neediest countries and capable of inducing herd immunity would save a disability-adjusted life year (or DALY) – a measure of quality of life gained and death averted – at an average cost of $35, according to a calculation by Dr Mark Miller. If the vaccine did not induce herd immunity, the cost per DALY would be $50. Dr Miller, a medical officer with the CDC and temporarily assigned to the CVI, made a number of assumptions for his analysis, including an annual incidence of over 3 million cases of Hib disease and 377,470 deaths in the developing world. Judging from the efficacy

Hib may be causing more than 600,000 pneumonia deaths a year – just about double the "working estimate" that health statisticians have been using so far.

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A nasty bug worth knowing about

Hæmophilus influenzae, so-called because health officials at the end of last century mistakenly believed it to be responsible for a massive flu pandemic, is a small, fragile rod-shaped bacterium, which at a certain stage in its life is enclosed in a capsule. The capsule, composed of a sugar (polysaccharide) molecule, comes in six types, from a to f, but type b is the one that causes most human disease.

Hib decided a long time ago to confine its parasitic preference to humans and its preferred nesting place, the nose, mouth and throat (upper respiratory tract). There it multiplies and from there sends out infective bacterial hordes into the air to find other victims.

Pneumonia and meningitis are the most frequent and often deadly consequences of Hib infection. Pneumonia can occur when the bacterium moves or is sucked from the upper into the lower respiratory tract, meningitis when it invades the bloodstream and travels to the brain.

Up to 30% of children who survive an episode of severe Hib meningitis suffer chronic neurological disability, ranging from hearing loss to mental retardation. Hib pneumonia saddles about 1% of its surviving victims with chronic respiratory problems, including bronchial dilation (bronchiectasis) and other residual damage.

Vaccination prevents not only acute episodes of Hib pneumonia and meningitis but also these chronic sequelae, as well as other potentially disabling – although less frequent and less life-threatening – forms of Hib disease. These include inflammation of the mouth (especially the epiglottis), the tissues around the eyes (periorbital tissues), joints (septic arthritis), skin (cellulitis), bones (osteomyelitis), and the membranes around the heart (pericarditis) and the lungs (empyema). Hib can also cause distressing but rarely fatal inflammation of the middle ear (otitis media, a cause of hearing loss), sinuses (sinusitis) or bronchi (bronchitis).

of the vaccine in industrial countries, the vaccine, he estimated, would prevent 2.5 million cases and 310,000 deaths and save $105 million annually in hospitalization and treatment costs. Certainly, if the figures for Hib cases and deaths are to be doubled, as Dr Kim Mulholland believes (see above), the cost of achieving those savings and of gaining DALYs would be less. But even at $50 a DALY, the Hib vaccine would be a good buy, according to World Bank analysts (see reference 4, page 14).

How realistic though is the $1-a-dose assumption for the neediest countries?

The four conjugate vaccines licensed in the U.S. carry a public sector price of $4.60 a dose. Production costs alone are somewhere between $1 and $1.50, including royalties. Certainly the conjugation process makes the newer Hib vaccines more expensive to manufacture – and to "quality control" – than traditional vaccines, but the selling price could fall, if...

► *if the potential market for the vaccine in the developing world is realized.* About 100 million doses of Hib conjugate vaccine will be needed in total over the next five years for the annual Third World cohort of 119 million infants under five, according to a very preliminary estimate by Dr Julie Milstien, a scientist with the GPV's vaccine supply and quality unit (VSQ). Thereafter, as the number of Hib-using countries reaches its full complement, 350 million doses a year will probably be needed, Dr Milstien believes. With a market this size, industry, over time, should be able spread fixed costs over a relatively large output and thereby reduce unit costs. The fact that several manufacturers are in the running for this market – and that some local Third World producers could even join the pack, despite the technological complexity of the manufacturing process – may help to push down prices.

► *if the EPI adopts the new vaccine.* The EPI is examining several new vaccines waiting in the wings for a decision. The Hib conjugate vaccine is one of them. Some managers of

A step-by-step game plan to get the Hib vaccine into the developing world by the year 2000

	ACTIVITY	SCHEDULE				
		1996	1997	1998	1999	2000
Disease Burden	Better define burden of Hib (and pneumococcal) disease					
Effectiveness	Protocol for safety and immunogenicity studies					
	Additional effectiveness studies					
	Evaluate reduced-antigen vaccine formulation					
	Evaluate combinations with pneumococcal vaccines, etc.					
Introduction	International meeting on Hib vaccination					
	Protocol for cost-effectiveness studies and support to use					
	Support and monitor 'early-adoption' countries					
	Regional and national discussions on introduction					
	"Awareness" activities to promote Hib introduction					
Supply	Situation analysis on availability of different Hib vaccine formulations					
	Establish desired product specifications					
	Quality control requirements					
	Tiered pricing, procurement by UNICEF and funding; other supply options					
	Estimate global demand from estimated national demand					

This plan is part of a document – An agenda to expedite global prevention of *Hæmophilus influenzæ* type b (Hib) disease – *drafted with help from many individuals, including experts with the WHO's Division of Child Health and Development (CHD), the WHO's Global Programme for Vaccines and Immunization (GPV), the U.S. Centers for Disease Control and Prevention (CDC) and the U.S. Agency for International Development (USAID). The document is still provisional and will be reviewed at a CVI meeting of all interested parties, including industry officials, to be held later this year. The CVI welcomes comments. If you wish to receive the full document, contact Dr Roy Widdus, CVI Coordinator, in Geneva, Switzerland, by fax (+41.22/791.48.88) or e-mail (cvi@who.ch).*

national immunization programmes, however, have expressed the fear that the EPI immunization system has enough on its hands trying to get the hepatitis B and yellow fever vaccines off the ground without having to deal with a newcomer.

► *if UNICEF buys into the operation.* UNICEF's brand new procurement strategy and "bundled" tender (see *CVI FORUM* No. 10, October 1995, page 10, and No. 11, *Special Industry Issue*, June 1996, pages 13-18) could enable industry to offer, say, a dollar-a-dose price for the neediest countries and proportionately higher prices for the richer markets that would help to cover research and development costs (the new tender has

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M. Weber

PAIN FOR A WORTHY CAUSE: *Chilean infant being vaccinated*

already produced an offer from Pasteur Mérieux-Connaught – conditional on a sizable purchase of DTP – of several million doses of free Hib conjugate for research on introducing it into developing countries).

► *if one or more cost-cutting strategies currently being researched are successful.* Before work started on the Hib agenda, researchers, many supported by the GPV, had begun to look for ways of reducing the cost of Hib vaccines. One way, for example, might be to reduce the number of doses administered: two doses instead of three might be sufficient. Or perhaps, where the Hib vaccine is given together with DTP, it could be left out of the first of the customary three doses of DTP but be included with the second and third doses: the idea would be to use the first dose of DTP – which contains a diphtheria or tetanus toxoid – to "prime" the recipients' immunity to a Hib PRP-tetanus toxoid or PRP-diphtheria toxoid vaccine given with the second and third DTP doses. Another tack would be to manufacture a synthetic (and less expensive) PRP to replace the natural molecule currently used in the conjugate vaccines: some researchers and manufacturers are exploring this option. Then again, it might be possible to reduce the amount of PRP antigen in the vaccine, without lowering its protective efficacy.

Whether any or all of these cost-cutting exercises work, one thing is sure: vaccine costs tend to fall as refinements are made to the production process over time. The recombinant hepatitis B vaccine, for example, which sold at over $40 a dose when it became available in 1986, took a decade to fall below $1 a dose for developing countries. Should we just wait passively for the price of the Hib vaccine to take its natural downward course? With hundreds of thousands of children dying every year, it's hardly an option.

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Which is why the Hib agenda plans a careful look at ways of helping countries to obtain the vaccine as quickly as possible. They include a tiered pricing scheme (for the different tiers or levels of purchasing power of the different countries), with the actual prices per tier worked out between producers and purchasers, including UNICEF for the neediest countries. Tiered pricing is already a widely accepted part of the global vaccine supply system. More innovative would be a system being mooted of tiered royalties that would have to be worked out with industry, particularly the biotech industry. Then, of course, countries could be helped to produce their own vaccine (although IPRs and complex biotechnology could disqualify most Third World manufacturers) or, more likely, to

form partnerships or other agreements (e.g. for bulk filling, packing etc.) with suppliers in industrial countries.

The CVI and the Rockefeller Foundation plan to hold a meeting next February in Bellagio, Italy, where economists, legislators, industry executives, technology managers and other players on the licensing arena will discuss these and other options.

How to turn need into demand and demand into action?

Public health pundits have little doubt that Hib is inflicting a heavy burden of disease and death on developing countries and that the Hib vaccines can alleviate, if not altogether free them from, that burden. The task of the CVI and its collaborators, as outlined in the Hib agenda, is to demonstrate that need clearly and to enlist the forces within countries that can identify where that need is greatest.

But awareness of the need will not necessarily create a demand for the vaccine. As experience with the hepatitis B vaccine has shown, the essential ingredient is commitment by public health policy makers and politicians. And political commitment, as experience with AIDS has shown, comes when enough noise – call it advocacy or education, if you like – is made about the need, locally, where it is felt most urgently. And advocacy is high on the Hib agenda's priorities.

Through high-profile international, regional and national meetings and other advocacy mechanisms, the CVI and its partners will attempt to rope in to the cause as many key players as possible. A major international meeting will bring them together early next year. On the demand side, participants will include national government officials, managers of immunization programmes, non-governmental organizations, academic institutions and local activity groups. On the supply side, the CVI will seek the participation, among others, of donor agencies, governments and national control authorities, vaccine manufacturers and international health and development agencies.

Enough noise, of the right sort, at the right time, in the right places, could hasten the day, as British physician and disability expert Sir John Wilson said, "when people will demand the right to immunization with the same passion with which they now demand the right to vote."

That is especially true of Hib immunization.

[1] *Development, Evaluation, and Implementation of Hib Vaccines for Young Children in Developing Countries: Current Status and Priority Actions, May 1996. (Not yet published formally, but available in draft form from the CVI secretariat.)*

[2] *The Jordan Report, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA, 1995.*

[3] *MMWR, Centers for Disease Control and Prevention (CDC), 44: 545-550, 1995.*

[4] *Copies of the document (ordering code WHO/VRD/GEN/95.05, 1995) may be obtained free of charge from VRD (fax: +41.22/791.48.60), which welcomes comments or suggestions.*

[5] *Large-scale, post-licensure, selective vaccination of Chilean infants with PRP-T conjugate vaccine: practicality and effectiveness in preventing invasive* Hæmophilus influenzæ *type b infections, R. Lagos* et al., Pediatric Infectious Disease Journal, *(15):216-222, 1996.*

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Plant vaccines: edible, but how credible?

Whether or not they ultimately fulfil their promise, edible vaccines have, since their début in the scientific literature in 1992, certainly given headline writers a field day: "Vaccine cuisine;" "Vaccine A-Peel;" and so on. In the interview below, Dr Charles Arntzen, pioneer and protagonist of this novel technology, gives a foretaste of its possibilities. Dr Arntzen is President and Chief Executive Officer of the Boyce Thompson Institute for Plant Research and Adjunct Professor of Biological Sciences at Cornell University, Ithaca, NY, USA.

Once inside a plant's genetic machinery, or DNA, the genes force the plant to produce the vaccinating antigens we're interested in.

Q *What are edible vaccines?*

A Vaccines contained in edible plants. The plants are genetically engineered to carry genes from disease causing microbes. Within the microbes, these genes control production of molecules, or antigens, known to provoke an immune response in people infected with the microbes. Once inside a plant's genetic machinery, or DNA, the genes force the plant to produce the vaccinating antigens we're interested in.

Q *So the plants would really be vaccine factories?*

A Not just factories but also vehicles, or vectors, to carry the vaccines into a person's body when they're eaten.

Q *Plants would not be the first living organisms to be used as vaccine producers or vectors.*

A No, but the first to be used both to produce *and* to deliver vaccines. Yeast is used by vaccine manufacturers to make the antigen incorporated in the recombinant hepatitis B vaccine licensed in the U.S. It is in fact the only microbe approved thus far by health authorities to produce antigens for human use. The common gut bacterium *Escherichia coli* is also used to make many vaccine antigens, but they are still experimental. And a number of microbes are being explored for their potential solely as vaccine vectors, such as BCG, the bacillus used to protect against tuberculosis, or *Salmonella*, that causes typhoid fever, or even human viruses like the polio virus, or adenoviruses that cause upper respiratory disease or the vaccinia virus, that is used to make the smallpox vaccine.

Graphic Communications Group

Dr Charles C. Arntzen

Q *What plants are suitable as vaccine producers and vehicles?*

A Obviously, first choice goes to those that are tasty and cheap and that can be eaten raw, since heat would inactivate protein antigens. Those conditions would rule out the tobacco leaves and raw potatoes of early experiments, which are not exactly sellouts with babies. But we recently showed that foreign genes can be inserted into banana DNA, and bananas are as baby-friendly as they are plentiful.

Q *Can any vaccine against any disease be produced in a plant?*

A The choice of antigens is limited to those we know elicit protective immunity when administered orally, those for which the genes have been cloned and those which retain their immunity stimulating, or immunogenic, properties when they emerge from the plant's genetic assembly line. We also have to be careful to choose antigens whose corresponding genes are not likely to be damaged in a plant's genetic processes or by any tinkering we have to do to ensure the maximum yield of good quality vaccine by the plant.

Q *Is the technology new?*

A Not at all. The first successful splicing of foreign genes into plant DNA goes back to 1983. Today, there are more than 40 different species of genetically engineered food, many of them being tested for human consumption. What's new is the use of that recombinant biotechnology to make plant vaccines.

Q *What advantages would plant vaccines have over other vaccine delivery methods?*

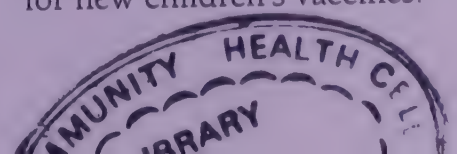
A Each of the 125 million children entering the world every year needs up to 16 doses of vaccine (one each of BCG, measles and yellow fever, three each of DTP, hepatitis B and *Hæmophilus influenzæ* type b, and four of oral polio). That's 2 billion doses of vaccine needed per year. Realistically, I'd say one banana can hold 10 doses of vaccine. So, we're going to need about 200 million bananas or 20,000 tons (at about 10,000 bananas per ton) to vaccinate all the world's children. That's a fraction – about a 450th or 0.2% – of the 9 million tons of bananas produced worldwide every year. Whatever the numbers of plants needed, however, growing fields of them should be a cheaper source of vaccine than the microbial fermenters used in today's vaccine production facilities.

Q *Why cheaper?*

A Recombinant vaccines are made today in various types of fermentation systems, including animal cells infected with microbes. These cells are at risk of infection with animal viruses that could contaminate the vaccines, which therefore have to go through a careful and costly purification process. Purification for viral contaminants wouldn't be necessary with plant vaccines since plant viruses can't infect humans. For another thing, bacteria undergo a lot of genetic changes during the fermentation process: careful and costly quality control is needed to make sure the resulting antigens correspond to standard specifications. Plant genes go through a lot of cycles but are exposed to far less pressure than microbes are in fermenters and are therefore extremely stable. What's more, plant vaccines wouldn't need costly refrigeration as many of today's vaccines do. You'd just need to grow the plants close to where the vaccines are used. Which illustrates yet another advantage: plants can be grown anywhere, cheaply, in the developing world and the vaccines just need to be harvested with the fruit or as crops, whereas many vaccines, particularly the newer, more complex ones, require sophisticated technology that only a few developing countries have access to.

Q *Other advantages of plant vaccines?*

A Three major ones. The first is that plants can be fitted with a very large number of foreign genes. The record is 150, so far. Another is that being in food these vaccines would be administered orally. And a third is that if our early findings in mice are borne out in human trials, plant vaccines should be capable of stimulating not only the more general antibody and cellular immunity needed for protection against most disease-causing microbes but also the local immune system of the gut, so-called mucosal immunity, which is probably the ideal, first-line defence against many diarrhœa-causing microbes. And by the way, these three assets – multiple target diseases, oral administration and induction of mucosal immunity – are three CVI priorities for new children's vaccines.



Plants can be grown anywhere, cheaply, in the developing world and the vaccines just need to be harvested with the fruit or as crops.

Graphic Communications Group

Mice nibble their daily vaccine dose

Q What have your studies of plant vaccines shown so far?

A To date, we have engineered tobacco plants to produce the hepatitis B surface antigen: the plant antigen seems almost identical to that used in the current recombinant hepatitis B vaccine and mice inoculated with leaf extracts from the plants show the full immune response seen in humans vaccinated with the hepatitis B vaccine. We've also engineered potatoes to produce an antigen of a particularly toxic (enterotoxic) form of *Escherichia coli* (ETEC) responsible for a lot of the diarrhoeal disease in developing countries – and mice showed immunity to the antigen after eating the raw potatoes. Another common cause of diarrhœa, especially in the industrialized world, is the Norwalk virus: we have inserted into potato plants the gene coding for the protein making up the outer shell, or capsid, of that virus and again, mice eating the potatoes have shown immunity.

Q Protective immunity?

A That is the big question. The mice studies we have conducted to date don't answer it, because mice don't get the infections we're talking about – with hepatitis B, ETEC or Norwalk virus. One study we did – but haven't yet published – showed that antibodies taken from mice that had been fed potatoes containing an ETEC antigen are capable of neutralizing the bug's toxin. It doesn't prove protection but it's encouraging. And of course we could use chimpanzees to study our hepatitis B plant vaccine – at a cost. But in the end, only human trials will be able to show true protection and – perhaps more importantly – how long that protection lasts.

Q How far are you from human trials?

A We will this summer be applying to the U.S. Food and Drug Administration (FDA) for authorization to conduct trials on volunteers, that could take place before the end of this year.

Q Are other groups working on edible vaccines?

A Not to my knowledge. But several are exploring the potential of plant viruses as vectors to deliver a variety of vaccinating antigens against, for example, malaria, AIDS, tooth decay, and even as contraceptive vaccines. Then there are groups using plants to produce not vaccinating antigens but antibodies, used for "passive immunization" against cholera, for example, or animal illnesses, like foot-and-mouth disease, or as homing devices for anti-cancer drugs.

In the end, only human trials will be able to show true protection and – perhaps more importantly – how long that protection lasts.

Q *All this sounds too good to be true. Any downsides?*

A Well, there are types of vaccines that plants won't be able to produce. I'm thinking, for example, of the conjugate vaccines, which get their strong immunogenicity by linking an antigen to an immunogenic protein through a fairly complex biochemical conjugation process (see page 2). But in any case we don't see plant vaccines as a substitute for vaccines obtained by other means but as an alternative source particularly suited to local Third World production.

Q *Do you see any major hurdles on the road ahead?*

A There are certainly hurdles to be overcome. For example, human trials would have to show that plant vaccines ingested with food will stimulate local gut immunity rather than dampening it through a mechanism of so-called immune tolerance. This mechanism makes a natural breach in the immune system through which the body allows food to be absorbed from the gut.

Then, the regulatory scene could be pretty complex. This is virgin territory for regulatory authorities, who will have to work out which particular section – drugs, foods, agricultural technology, or whatever – should be licensing these edible vaccines. And which component of the vaccine they need to license as safe and effective: the antigen? the genetically engineered fruit or crop? the seeds?

Then there's the problem of dosage. We will be able to measure the antigen content of foods, but we have to be sure that growth conditions in other parts of the world don't cause changes in antigen accumulation.

One hurdle could also be the anti-biotech climate in some countries, like the U.S. or Germany, that could force governments to tighten regulatory requirements for plant vaccines.

Q *These hurdles sound quite daunting.*

A With time and growing experience of plant vaccine technology, they should become less formidable. Don't forget, the whole idea is only four years old. We're still in the very early stages of developing that idea. Right now the prospects are exciting. We'll handle the hurdles when we come to them. Or, we'll just call on the folks at the CVI to handle them!

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Note 1: The transgenic plant work being conducted by Dr Arntzen's group is supported by grants from the Thrasher Foundation, the WHO, the World Bank and the U.S. National Institutes of Health (NIH).

Note 2: the CVI plans to hold a meeting of experts within the next 12 months to discuss the potential of this technology.

We're still in the very early stages of developing that idea. Right now the prospects are exciting. We'll handle the hurdles when we come to them.

HOW COST-EFFECTIVE WOULD A VACCINE BE AGAINST...

Schistosomiasis

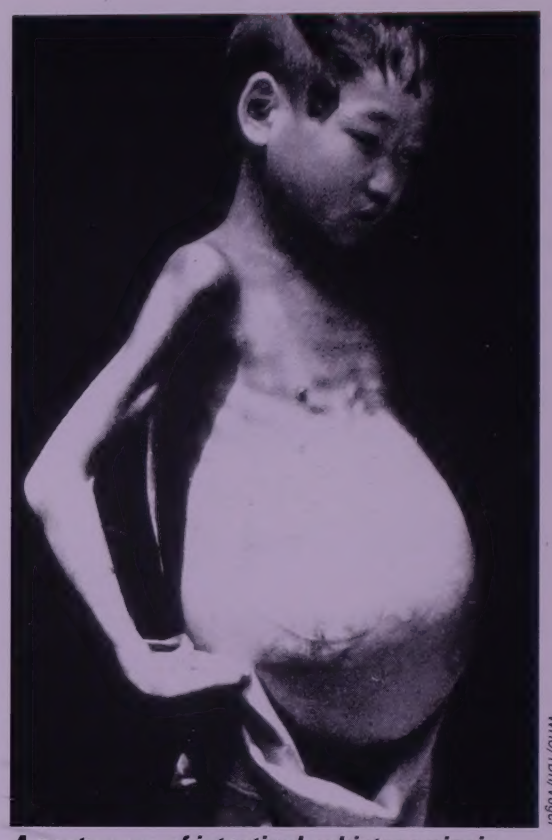
An estimated 20 million people suffer severe disease or disability from schistosomiasis at any given time and about 50,000 die from the disease every year. An inexpensive and effective drug, praziquantel, exists but the risk of reinfection following treatment is high and calls for long-term annual retreatment.

Work on developing a vaccine has uncovered several immune-stimulating molecules (antigens) in one of the worm species, *Schistosoma mansoni*, that cause human disease. Six of these antigens have been tested in animals for their protective potential as vaccines or vaccine components, with inconsistent and on the whole disappointing results. Tests, however, of their ability to produce immune responses indicative of protection in people living in endemic areas are showing promise.

Work on developing a vaccine has uncovered several immune-stimulating molecules (antigens) in one of the worm species that cause human disease.

A schistosomiasis vaccine used in an area where the disease is highly prevalent in a low-income country, administered to at least 80% of children in the area and providing protection for at least 90% of those receiving the full dose would cost US$64 to US$405[1] per DALY[2] (more or less equivalent to a healthy year of life) saved. Three conditions, though: the vaccine's protective effect must last for at least 10 years, its cost must not be more than US$5 per completely vaccinated child, including delivery (over-and-above the cost of current EPI vaccines[3]), and it must be delivered through the EPI system.

Such a schistosomiasis vaccine would be relatively cost-effective compared with mass chemotherapy (with praziquantel) for youngsters aged 6 to 15 years, which would cost US$431 to US$1,732[1] per DALY saved. Note that the oral polio vaccine plus the diphtheria-tetanus-pertussis (DTP) combination costs US$20 per DALY saved, the measles vaccine US$2-15 and the hepatitis B vaccine US$25-50.[4]



WHO/TDR/Vogel

A nasty case of intestinal schistosomiasis

If however the protective effect of a schistosomiasis vaccine lasted only 1-2 years and it could not be delivered through the EPI system, its cost per DALY saved would be US$548-10,567 and it would therefore not be a cost-effective vaccine compared with treatment.

This article is based on a cost-effectiveness analysis by the UNDP/WORLD BANK/WHO Special Programme for Research and Training in Tropical Diseases (TDR).

[1] *The range depends on upper and lower limits of a number of variables, such as the value (weight) given to disability, the cost per child per year of chemotherapy, the cost of delivering the vaccine and the duration of protection it gives.*

[2] *A DALY, or disability-adjusted life year, gives a measure of the combined loss of quality of life through disease or disability and loss of life itself.*

[3] *The EPI (Expanded Programme on Immunization) system, implemented by national immunization programmes, currently delivers a basic "package" of vaccines against pertussis, polio, diphtheria, measles, tetanus and tuberculosis to about 80% of the world's children).*

[4] *according to* D.H. Jamison et al, *eds.* Disease control priorities in developing countries. *Oxford, Oxford University Press (for the World Bank), 1993, who consider a cost less than US$25 an excellent buy and between US$25 and US$250 a good buy.*

Future CVI Meetings

9-10 December, 1996, Dakar, Senegal

CVI Consultative Group Meeting

Africa is the site of this year's CVI Consultative Group meeting, which is hosted by the Senegalese government. Participants include

representatives of industry, national immunization programmes, non-governmental organizations, international organizations, the donor community, scientific institutes and national health ministries. Topics of plenary sessions and workshops will include: *Commitment as the key to expanding immunization, Update on polio eradication, Advocacy for vaccines and immunization, Vaccine procurement, Vaccine financing, New priority vaccines for Africa,* and many others (see also page 16). For further details contact Ms Molly Abruzzese, CVI Consultative Group Coordinator, by fax (+41.22/791.48.88) or e-mail (cvi@who.ch).

31 October-1 November, 1996 (dates tentative), Geneva, Switzerland:

Developing an agenda for the global introduction of a rotavirus vaccine

Notes from past meetings

Stable OPV work halted

At a meeting held on February 7-8, 1996, members of the CVI's product development group (PDG) on thermostable oral polio vaccine recommended that the PDG be disbanded. This recommendation, which was accepted, stemmed primarily from doubts about the need for a more stable vaccine given the progress being made in eradicating polio with existing vaccines. The current introduction of vaccine vial monitors and concerns about the possible negative impact of a novel formulation on public acceptance of the vaccine also played a role in the decision. Meeting participants noted that the work of the PDG had produced useful lessons, among other things, in working with vaccine manufacturers.

CVI Publications

Available free of charge from the CVI Secretariat. Please indicate the title and ordering code (shown in brackets).

- CVI Secretariat: Report on 1995 Activities [CVI/GEN/96.04]
- CVI Secretariat: Financial report on the biennium 1994-1995 [CVI/GEN/96.05]
- Proposed CVI Secretariat Budget for 1996 and Tentative Budget for 1997 [CVI/GEN/96.06]
- An agenda to expedite prevention of *Hæmophilus influenzæ* type b (Hib) disease [DIP/96.19]
- An agenda to expedite global prevention of pneumococcal disease in infants and children. [DIP/96.21]
- Report of the Fifth Meeting of the CVI Consultative Group, São Paulo, Brazil, October 25-26, 1995. [DIP/96.13]
- *CVI FORUM* 10 (October 1995): Special progress report issue
- *CVI FORUM* 11 (June 1996): Special vaccine industry issue
- *CVI FORUM* 12 (August 1996)

Two CVI awards to mark "Year of the Vaccine"

The CVI has chosen this year, designated *Year of the Vaccine* in memory of Edward Jenner and Louis Pasteur, to create two prizes for vaccine-related work. The prizes, worth $10,000 each, will be awarded annually for recent contributions to immunization and to vaccine development, respectively. The prize-giving ceremony will take place during the annual CVI Consultative Group meeting, to be held this year on December 9-10 in Dakar, Senegal (see page 15).

The CVI secretariat seeks nominations for both awards. Nominees may be individuals, groups or institutions, but their nominations must be based on recent work and must include a written explanation (500 words maximum) justifying the choices of nominees and specifying which award should be given to a given nominee.

Nominations must be sent to: CVI Secretariat, c/o World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland or faxed to +41.22/791.48.88, to be received no later than October 1, 1996. A special sub-committee of the Scientific Advisory Group of Experts (SAGE) of the CVI and the WHO's Global Programme on Vaccines and Immunization (GPV) will select the prize-winners.

PICTURE POSTSCRIPT

Rollicking in the Gambian sun.

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